A 'Short' Feedback Mechanism Controlling FSH Secretion

It has recently been demonstrated that in addition to feedback mechanisms based on the interplay between the hypothalamic-pituitary complex and the peripheral target glands[1,2], other types of control systems exist in endocrinology. Feedback mechanisms completely independent of the hormones secreted by the peripheral target glands, and in which the inhibitory signal is provided by pituitary hormones themselves, have recently been described for the control of adrenocorticotropic hormone (ACTH)[3], of luteinizing hormone (LH)[4-6] and of other pituitary hormones (see MESS and MARTINI[7] for references). For these systems, the names 'short', 'internal' or 'auto' feedback mechanisms have generally been adopted.

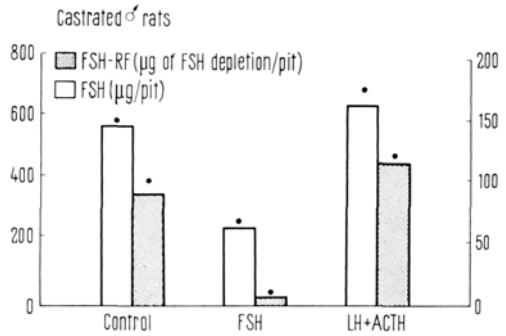
CORBIN[8,9] has reported that median eminence (ME) implants of follicle stimulating hormone (FSH) are effective in lowering pituitary FSH stores and the concentration of the hypothalamic factor controlling FSH secretion (FSH-releasing factor or FSH-RF); control ME implants of LH and bilateral amygdalar implants of FSH were without significant effects on the same parameters. These results have been interpreted to mean that a 'short' feedback mechanism may exist also for the control of the secretion of FSH and that the receptors sensitive to the inhibiting effect of FSH are located in the ME. However, because of several potential limitations inherent in implantation techniques, other interpretations are also possible. For instance, any time a hormone is implanted in the brain, certain nervous structures have to be lesioned in order to allow the passage of the needle, so that the results obtained are the algebraic sum of a non-specific effect (lesion effect) and of the specific effect of the material implanted. Moreover, when the area which is explored is the ME, the possibility exists that the compound implanted is transported and distributed to the anterior pituitary through the portal vessels: in this case the effect observed might be due to an action on pituitary cells rather than on structures belonging to the central nervous system; this possibility has been stressed in recent years mainly by BOGDANOVE[10]. In addition, CORBIN'S[8,9] experiments were performed on normal animals with their gonads in situ, so that it cannot be excluded that some FSH was absorbed into the systemic circulation; this may obviously have elicited the release of gonadal steroids and the inhibition of FSH and FSH-RF secretion through the classic (steroid) feedback mechanism[11].

In order to overcome all these difficulties, it was decided to study whether the treatment of castrated male rats with exogenous FSH might bring about some modification of pituitary stores of FSH and of hypothalamic stores of FSH-RF.

Male rats of the Sprague-Dawley strain (average body weight 150 g) were castrated; in 1 group of 10 animals treatment with FSH was begun 3 weeks after the operation; treatment was continued for 5 days, administering s.c. the daily dose of 20 μg of ovine NIH-FSH-S_3. Two groups of castrated controls (10 rats/group) were used: one was given saline, the other one was treated with a mixture of ACTH plus LH for 5 days. Four identical experiments were performed. After sacrifice, the FSH content of the pituitaries of the different groups of animals was measured in homogenates of pooled glands by using the ovarian augmentation test of STEELMAN and POHLEY[12] as modified by PARLOW and REICHERT[13]. A 2 + 2 design was adopted against a standard of FSH (NIH-FSH-S_3, ovine); 3 assay animals were used for each point. The index of precision (λ) and the relative potency were calculated by the methods recommended by GADDUM[14]. The FSH-RF activity present in the hypothalami of the different groups of rats was quantitated according to the procedure of DÁVID, FRASCHINI and MARTINI[15]. This is based on the ability of hypothalamic extracts to deplete pituitary FSH stores when injected into the carotid artery of normal recipient male rats; an amount of hypothalamic tissue corresponding to $^3/_4$ of a hypothalamus was routinely injected into each recipient animal.

The data summarized in the Figure clearly indicate that treatment with exogenous FSH results in a significant drop in pituitary stores of FSH and in the hypothalamic content of FSH-RF. None of these effects was obtained when LH + ACTH was injected.

These data, which confirm CORBIN'S[8,9] results from another approach, apparently indicate that high plasma levels of FSH may reduce the secretion in further amounts of FSH through a 'short' feedback loop; the data also indicate that this happens because the synthesis and the storage of FSH-RF are inhibited. Apparently, the



Effect of s.c. administration of FSH on the pituitary content of FSH and on the hypothalamic concentration of FSH-RF. Columns represent the mean of the results obtained in the 4 experiments performed. Dots indicate the standard error of the mean. The scale on the left side refers to FSH values; the scale on the right side refers to FSH-RF values.

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inhibitory signal provided by FSH is very specific; it has been impossible to duplicate it by using 2 other pituitary hormones (ACTH + LH).

These results and their interpretation are also supported by the data of NEGRO-VILAR and MEITES[16] and of CORBIN (personal communication, 1967) which have shown that hypophysectomy is followed in the rat by the appearance of measurable amounts of FSH-RF into the peripheral blood; treatment of hypophysectomized animals with pituitary FSH makes FSH-RF plasma levels disappear. Another recent result points to the same conclusion[17]: treatment of hypophysectomized-castrated rats with FSH has been shown to reduce the size of the nuclei of several hypothalamic cells[18,19].

Résumé. Les auteurs ont montré que l'administration s.c. d'hormone folliculo-stimulante (FSH) entraîne, chez le rat mâle castré, une diminution significative de quantités de FSH présentes dans l'hypophyse et de FSH-releasing factor (FSH-RF) stockées dans l'hypothalamus. Ces résultats suggèrent qu'un mécanisme de «short feedback» peut contrôler la sécrétion de FSH; ce mécanisme de «contre-régulation courte» agirait au niveau de l'hypothalamus.

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[19] The authors would like to thank the Endocrinology Study Section of the National Institutes of Health, Bethesda, Md., for the generous gift of FSH and LH preparations.

Chromosome Aberrations Induced by Daunomycin in Human Leucocyte Cultures, with the Apparent Synergistic Effect of Arginine

Daunomycin is an antibiotic isolated from *Streptomyces peucetius* (GRIEN et al.[1]) which has lately seen some success in experimental use against childhood leukemias and certain solid tumors (TAN et al.[2]). It is a glycoside with an aglycone chromophore linked to an amino sugar, which binds to DNA both in vivo and in vitro (GOLDBERG[3]). A few studies have been reported on the adverse action of Daunomycin on mitotic activity (DIMARCO et al.[4,5]). Cessation of DNA and RNA synthesis (DIMARCO[4,6], GOLDBERG[3]) and speculations on the role of Daunomycin in blocking other biochemical processes have been reported but there have been no reported studies on the action of this antibiotic on chromosomes except for negative results noted in HeLa cells (OSTERTAG and KERSTEN[7]). We may postulate that a drug which can cause cessation of DNA synthesis and inhibit protein synthesis (DIMARCO et al.[6]) may have the capacity to cause chromosomal aberrations. This paper reports confirmation of this postulate.

Cultured human leucocytes from 3 normal females were treated with Daunomycin during the last 12–48 h of a 72 h

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Table I. Analysis of chromosome aberrations induced by daunomycin

Treatment	No. of cells analysed	% of cells with aberrations	Frequency and types of aberrations		
			Fragments	Interchanges	Aberration frequency/cell
Control	100	0	0	0	0
Daunomycin μg/ml					
12 h 0.02 and less	100	0	0	0	0
24 h 0.01 and less	100	0	0	0	0
0.02	70[a]	57.1	60	92	2.17
48 h 0.01 and less	100	0	0	0	0
0.02 and more[b]	no mitosis				

[a] Only 70 cells were available for study. [b] Complete cessation of mitotic activity was observed with 0.03 μg/ml of Daunomycin for 12, 24, or 48 h.